THE biomarkers CONSORTIUM

October 28, 2009

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NIH Director for The Biomarkers Consortium

A Consortium Model For Biomarker Research

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NIH Director for The Biomarkers Consortium

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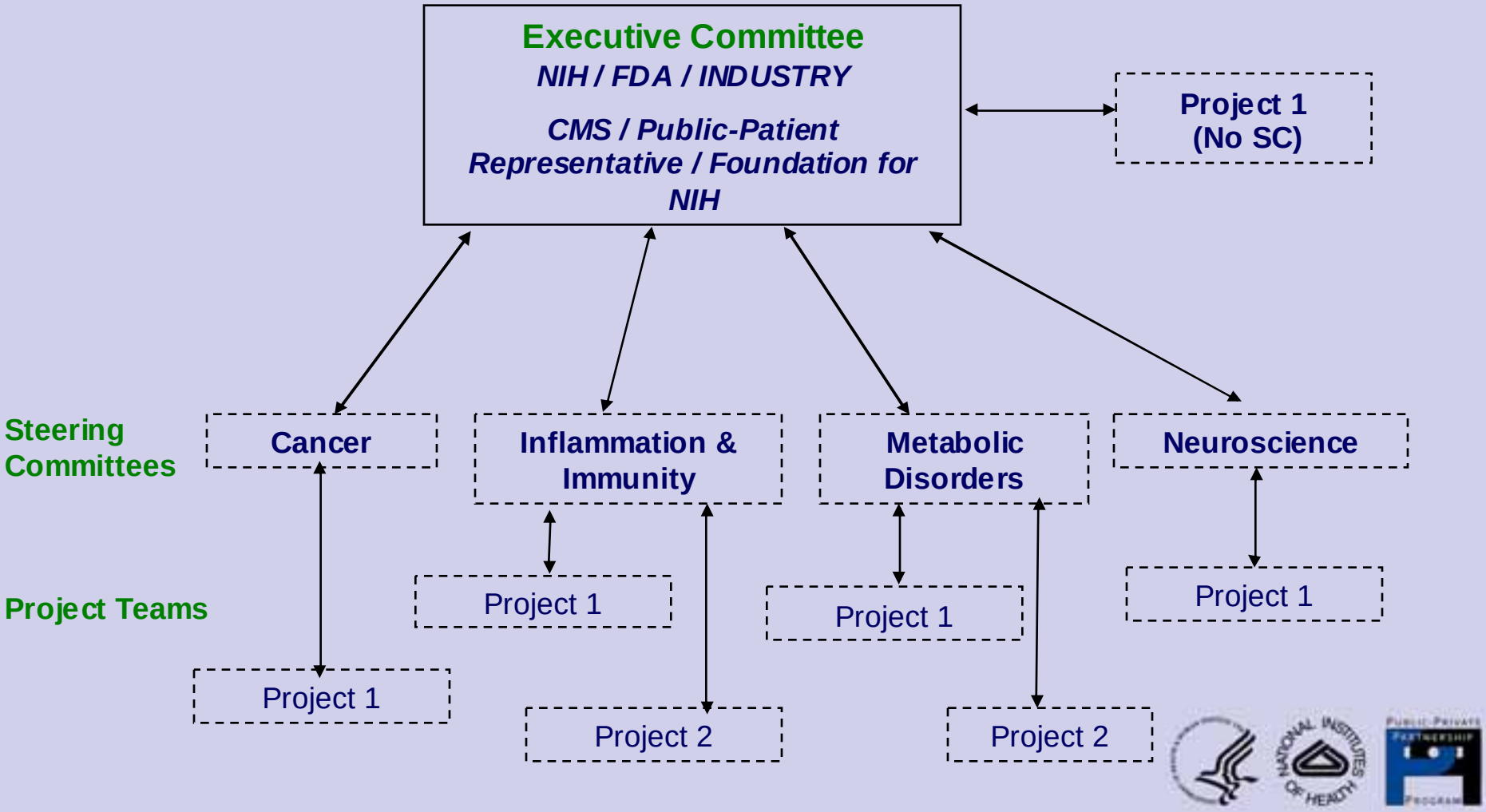
Goals of The Biomarkers Consortium

- Facilitate the discovery, development, and validation of biomarkers using new and existing technologies
- Help qualify biomarkers for specific applications in:
  - diagnosing disease
  - predicting therapeutic response
  - improving clinical practice
- Generate data useful to inform regulatory decision-making
- Make consortium project results broadly available to the entire scientific community -- "biomarker resources"

Governance Structure



The Biomarkers Consortium Executive Committee

Chairman
Charles Sanders, Foundation for NIH

NIH
Thomas Insel, NIMH
John Niederhuber, NCI
Lawrence Tabak, NIDCR

FDA
ShaAvhree Buckman,
Office of Translational Science
Dan Schultz,
Center for Devices & Radiological Health
Janet Woodcock,
Director of CDER

Public Member
Mary Woolley, Research!America

Centers for Medicare & Medicaid Services
Barry Straube

Industry
Stephen Eck, Eli Lilly & Co.
Gary Herman, Merck & Co., Inc.
Garry Neil, Johnson & Johnson
Sara Radcliffe, BIO

Foundation for NIH Board
Steve Paul, Eli Lilly & Co.
Ellen Sigal, Friends of Cancer Research

Steering Committee Co-Chairs

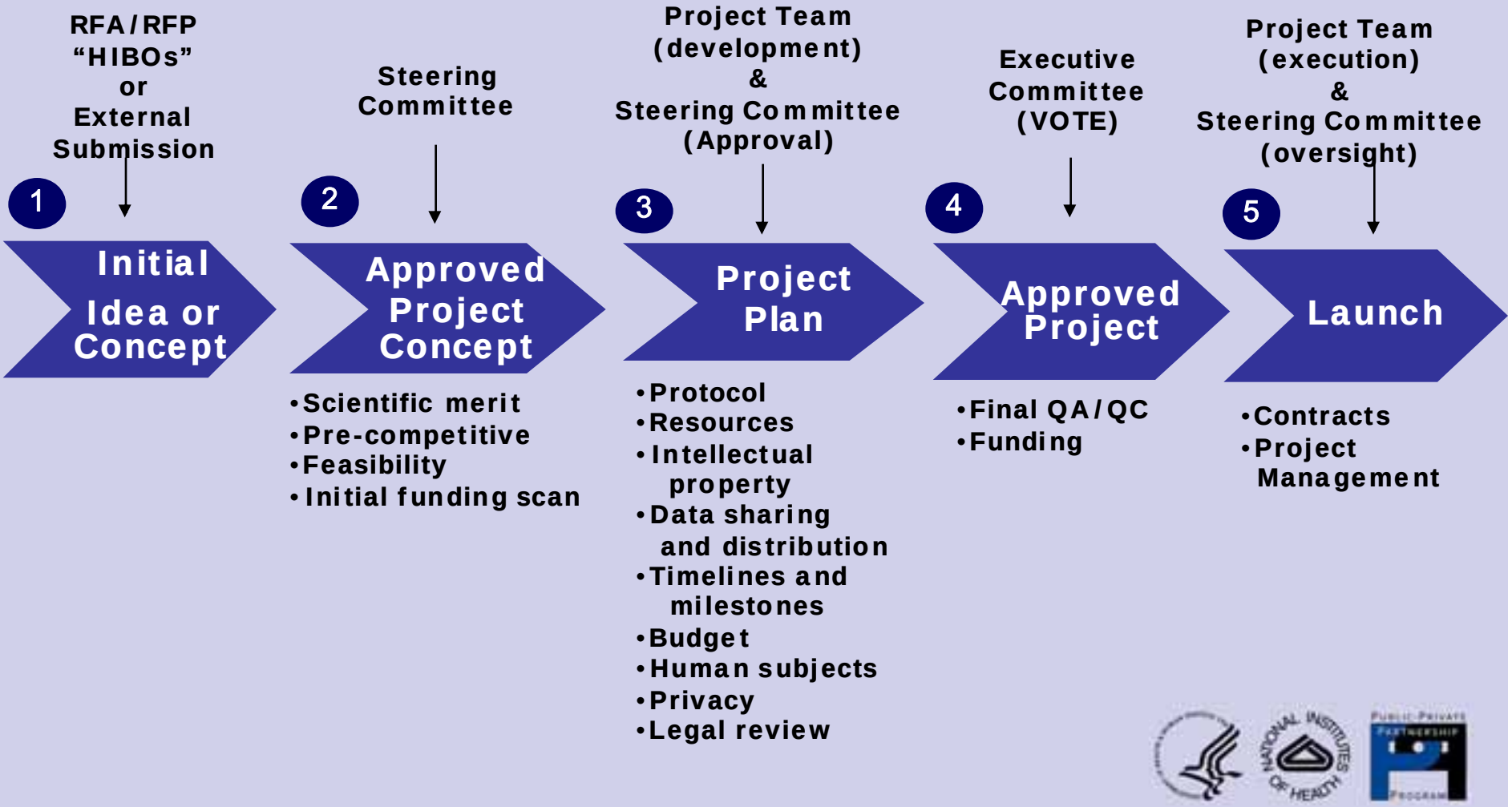
- **Cancer**
  - Anna Barker, National Cancer Institute
  - David Parkinson, Nodality, Inc.
- **Inflammation and Immunity**
  - Daniel Rotrosen, NIAID
  - Bruce Littman, Translational Medicine Assocs. (ex-Pfizer)
- **Metabolic Disorders**
  - David Kelley, Merck and Co., Inc.
  - Myrlene Staten, National Institute of Diabetes and Digestive and Kidney Diseases
- **Neuroscience**
  - Huda Akil, University of Michigan
  - William Potter, Merck and Co., Inc.

Principles and Policies

- Key governing policies have been pre-negotiated with the stakeholders (and their legal counsel) representing FNIH, NIH, FDA, PhRMA, CMS and BIO:
  - Antitrust
  - Confidentiality
  - Conflict of Interest
  - Intellectual Property
  - Data sharing
  - Grant Awards / Contractor Selection

Note: Policies, concept submission forms, and other information available at: www.biomarkersconsortium.org

Project Development Process



Project Selection Approach: *"High-Impact Biomarker Opportunities"*

Strategic focus on high impact areas of biomarker development and validation:

- ***Important:*** addresses a significant unmet/scientific need
- ***Translational:*** will result in significant improvement in the development, approval or delivery of care to patients
- ***Transformational:*** addresses critical gaps
- ***Feasible:*** end goals can be likely achieved in a specific timeframe
- ***Practical:*** leverages pre-existing resources wherever possible
- ***Fundable:*** is capable of generating the required funding/stakeholder support needed
- ***Unique:*** not already substantially being done elsewhere
- ***Collaborative:*** would uniquely benefit from the multi-stakeholder composition and approach of The Biomarkers Consortium

Contributing Members (49)

For-Profit Companies (19)	
Abbott Laboratories	Ingenuity Systems
Althea Technologies	Johnson & Johnson
AstraZeneca	Eli Lilly and Company
Avalon Pharmaceuticals	Luminex Corporation
BG Medicine, Inc.	H. Lundbeck A/S
Boehringer-Ingelheim Pharmaceuticals	Merck and Co., Inc.
Bristol-Myers Squibb	Metabolon, Inc.
Digilab Biovision GmbH	Novartis Pharmaceutical Corp.
EMD Serono, Inc.	Novo Nordisk
Genstruct, Inc.	Pfizer, Inc.
GlaxoSmithKline	F. Hoffmann-La Roche
GVK Biosciences	Rules-Based Medicine, Inc.
InfraReDx, Inc.	Scout Diagnostics
	Wyeth

Non-Profit Companies (30)	
Academy of Molecular Imaging	Avon Foundation
Advanced Medical Technology Association	Battelle Memorial Institute
Alliance for Aging Research	Biotechnology Industry Organization
Alzheimer's Association	CHDI Foundation
American Association for Cancer Research	Cystic Fibrosis Foundation Therapeutics
American College of Neuropsychopharmacology	Federation of Clinical Immunology Societies
American Health Assistance Foundation	The Hamner Institutes for Health Sciences
American Society of Clinical Oncology	The Immune Tolerance Institute, Inc.
American Society for Clinical Pharmacology and Therapeutics	Juvenile Diabetes Research Foundation
American Society for Therapeutic Radiology and Oncology	Kidney Cancer Association
Association of Clinical Research Organizations	The Leukemia and Lymphoma Society
Autism Speaks	Michael J. Fox Foundation for Parkinson's Research
Avon Foundation	Ontario Cancer Biomarker Network
Battelle Memorial Institute	Pharmaceutical Research and Manufacturers of America
Biotechnology Industry Organization	Radiological Society of North America
CHDI Foundation	Ryan Licht Sang Bipolar Foundation
Cystic Fibrosis Foundation	Society for Nuclear Medicine
	University of Illinois

Approved Projects to Date (15)

Project Name/Committee	Execution Objective	Status
FDG-PET Lung and Lymphoma Projects (CSC) ***Note: 2 projects***	**Build a case for FDA incorporation of FDG-PET into outcome measures for lung cancer and lymphoma.** Assess the use of FDG-PET as a biomarker for clinical trials conducted in non-small cell lung cancer and lymphoma. The overall goal of this project is to determine the linkage of FDG-PET, a promising imaging technology, to the effect of conventional cytotoxic drugs in clinical outcome and survival in two different tumor types.	Launched 1-2Q/2007; five year projects
Circulating Tumor Cells in Metastatic Prostate Cancer (CSC)	1. Validate CTCs as a marker of tumor progression and surrogate marker for survival in prostate cancer. 2. Evaluate new methods against the current FDA-approved CTC enumeration method.	Approved for execution Q4 2008 (11/2008)
DCE-MRI Technique Optimization Using Prostate Cancer as a Model System (CSC)	Establish a benchmark dataset that will enable development of a standardized approach to DCE-MRI, facilitating its use in clinical trials for new anti-angiogenesis agents	Approved for execution Q2 2009 (2/2009)
Detection and Characterization of Circulating Tumor Cells in Prospective Treatment Trial of *Neoadjuvant* and *Metastatic* Breast Cancer (CSC) ***Note: 2 projects***	Establish the technical, biological and clinical parameters necessary to evaluate the clinical utility of CTCs Develop language for CTC validation protocols Determine the clinical utility of CTCs in cancer drug development and patient management.	Approved for execution Q2 2009 (4/2009)

Approved Projects to Date *(continued)*

Project Name/Committee	Execution Objective	Status
PET Imaging of Inflammation in Rheumatoid Arthritis (Immunity & Inflammation SC)	Perform a feasibility study to determine the potential clinical utility of PET imaging as a biomarker to indicate active inflammation in RA	Approved for execution Q3 2009 (8/2009)
Adiponectin Project (Metabolic Disorders SC)	Determine whether adiponectin has utility as a predictive biomarker of glycemic control	Completed – publications released in July 2009
Carotid MRI Reproducibility Project (Metabolic Disorders SC)	Establish a standardized carotid MRI protocol and impact of site/platform on reproducibility	Launched Q3 2008; 18 month project
Sarcopenia Consensus Summit (Metabolic Disorders SC)	Generate a consensus definition of sarcopenia (age-related decrease in skeletal muscle mass) to provide specific guidelines for diagnosis/better enable regulatory decisions	First phase launched July 2009; two year project
Alzheimer's Disease Targeted Plasma Proteomics Project (Neuroscience SC)	Qualify a multiplexed panel of known AD plasma-based biomarkers using plasma samples from the Alzheimer's Disease Neuroimaging Initiative	Launched 12/2008; one year project

Approved Projects to Date *(continued)*

Project Name/Committee	Execution Objective	Status
PET Radioligand Project (Neuroscience SC)	Develop improved, more sensitive radioligands with higher binding to the peripheral benzodiazepine receptor	Launched 3/2009; two year project
Placebo Data Analysis in Alzheimer's Disease and Mild Cognitive Impairment Clinical Trials (Neuroscience SC)	Combine placebo data from large industry clinical trials and analyze them to provide better measures of cognition and disease progression for use in future AD/MCI clinical trials	Approved for execution Q2 2009 (6/2009)
Alzheimer's Disease Targeted CSF Proteomics Project (Neuroscience SC)	Qualify a multiplexed panel of known AD CSF-based biomarkers; examine Beta-Site APP Cleaving Enzyme levels in CSF; and qualify a mass spectroscopy panel as a tool to diagnose and monitor disease progression using CSF samples from the Alzheimer's Disease Neuroimaging Initiative	Approved for execution Q2 2009 (6/2009)
Metabolomics Signatures and Biomarkers for Depression and its Treatment (Neuroscience SC)	Conduct a comprehensive metabolomic analysis of soluble and lipid metabolites, including neurotransmitter-related metabolites, coupled with statistical analysis and data mining in order to identify metabolic signatures (biomarkers) that predict early and/or late response to SSRIs	Approved for execution Q3 2009 (8/2009)

Pipeline: Next Project

Project Name	Execution Objective	Expected Cost/Duration	Status
I-SPY-2 Adaptive Breast Cancer Trial [Cancer]	Breakthrough biomarker-based adaptive trial design in neoadjuvant setting in high-risk breast cancer patients	~$8-9 million / 5 years	September 2009 EC

Longer Term Pipeline: Project Teams/Working Groups

Activity	Execution Objective	Estimated Cost/Duration	Status
Markers of Immune Status Working Group [Immunity & Inflammation]	Develop robust testing platforms that can be used to monitor markers of immune function in clinical trials	$3-4M / 2 years	Working group formed; developing project plan
Atherosclerosis Working Group [Metabolic Disorders]	Use modeling approach to Identify a panel of Phase II biomarkers that predict Phase III outcomes in 6 months or less; second phase will identify subjects at higher risk than current risk engines via focused prospective trial	TBD	The working group's strategy document will be presented to the EC in June 2009
Beta Cell Function Working Group [Metabolic Disorders]	Develop a consensus statement on best current and potential approaches to assess beta cell function and factors that influence beta cell function ➔ specific project(s) to be defined	TBD	Symposium held on April 15-16, 2009; consensus statement under development that will be presented to the EC in August 2009

NIH Contact Information

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Current Active Projects:
Relative Industry to NIH Contributions

Project Name/ Committee/Duration	Private Sector Support (in $1,000s)	NIH Support (Grants & in-kind, in $1,000s)*	Grand Total	Cost Share: Industry %	Cost Share: NIH %
FDG-PET Lung and Lymphoma Projects (CSC – 60 months) [2 projects]	6,570 (9 funders)	3,750	**10,320**	**64%**	**36%**
Adiponectin Project (MDSC – 9 months)	0 (data sharing project)	0	**0**	**0%**	**0%**
Carotid MRI Reproducibility Project (MDSC – 18 months)	957 (3 funders)	1,020	**1,977**	**48%**	**52%**
ADNI Targeted Plasma Proteomics (NSC – 9 months)	450 (funded through ADNI surplus)	500	**950**	**47%**	**53%**
PET Radioligand Project (NSC – 24 months)	561 (6 funders)	500	**1,061**	**53%**	**47%**
TOTAL	**$8,538**	$5,770	**$14,308**		

**** Estimated***

Private Sector Participation in The Biomarkers Consortium

- Allows for the *leveraging of financial and scientific resources* from industry, government (FDA, NIH, CMS) and foundations and other non-profit organizations

- Industry participation offers new opportunities to:
  - maximize investment in clinical research programs
    - pool samples & data from completed trials
  - combine industry, government and academic expertise
  - "piggyback" onto existing research studies and clinical trials
  - spread financial and scientific risk
  - explore scientific basis for new regulatory pathways

Contributing Membership Program

- Provides operational funds to the Foundation for NIH to operate the Consortium
- Allows all sectors to participate in the activities of the Consortium

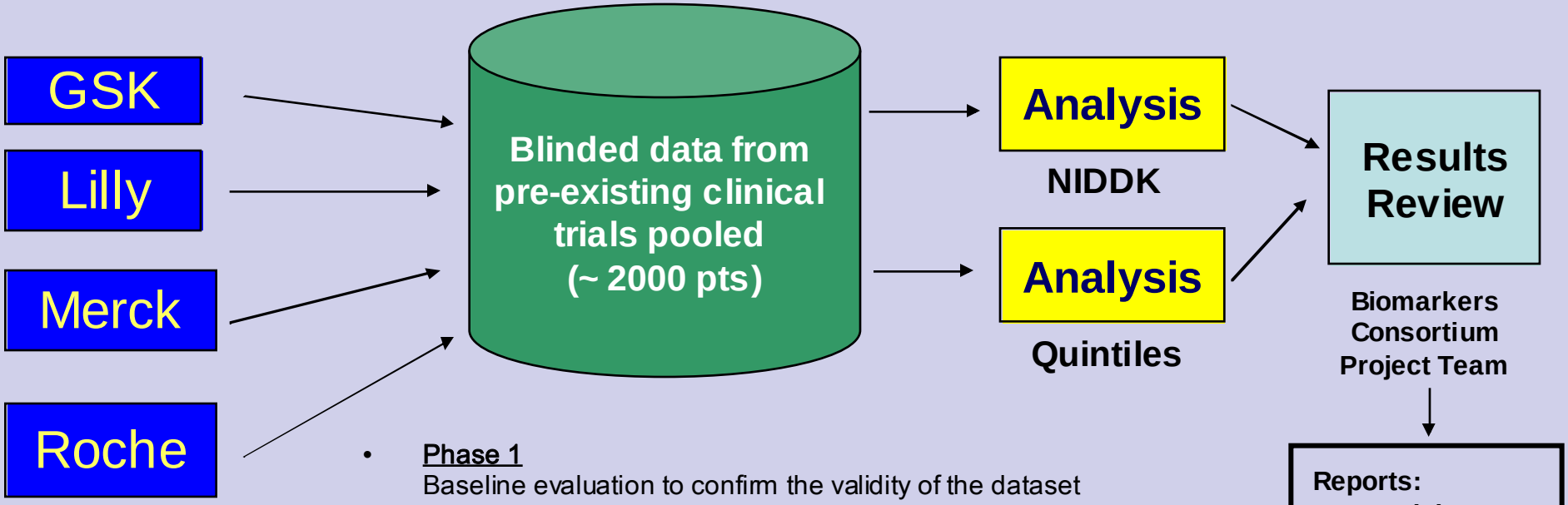
Membership Benefits

- Elect three (3) representatives to serve on the Executive Committee
- Nominate individuals to serve on Steering Committees (created to date in cancer, immunity & inflammation, metabolic disorders, and neuroscience) and Project Teams (developing individual projects)
- Participate in “high-impact biomarkers” prioritization process
- Propose project concepts and ideas for potential Consortium execution

Annual Membership Dues

- Companies: $5,000-$100,000 per year (depending on annual sales)
- Non-profits: $5,000 per year

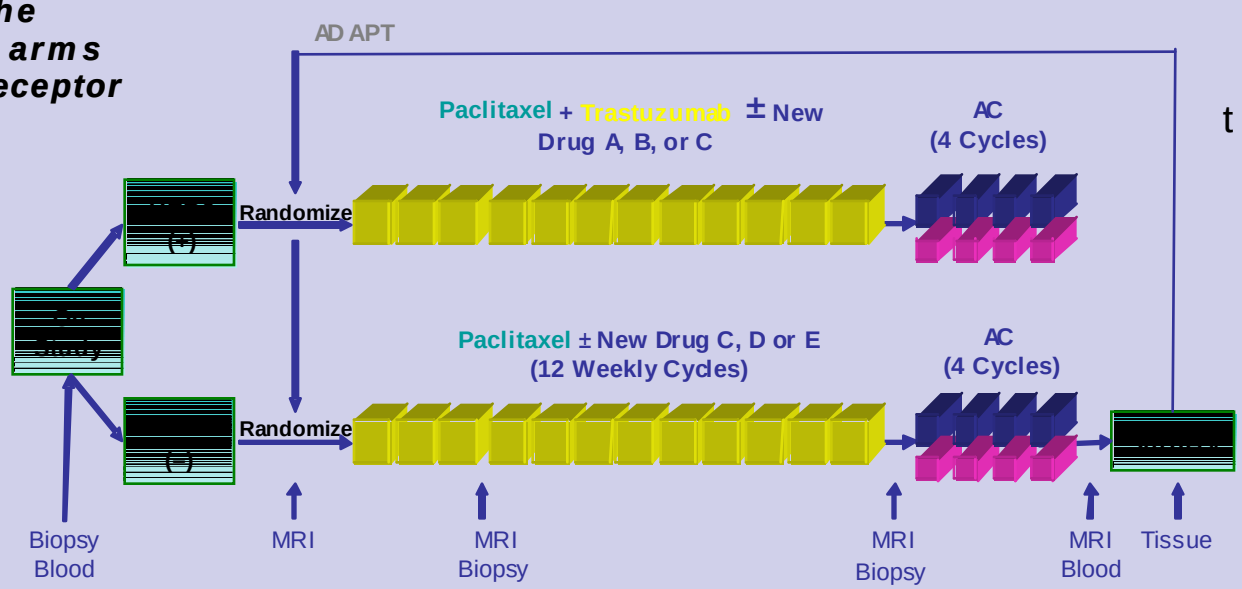
Adiponectin Project: Study Design



- <u>Phase 1</u>
  Baseline evaluation to confirm the validity of the dataset
- <u>Phase 2</u>
  Evaluate change of adiponectin vs. change of the other variables
- <u>Phase 3</u>
  Examine prognostic value change in adiponectin at "early" times to predict HbA1c response

I-SPY TRIAL 2 uses an adaptive trial design to identify successful treatment regimens for Stage II/III breast cancer based on specific biomarkers

Step 1: Stratify the patients into two arms based on HER2 receptor status



Stratifying Biomarkers:

Class I/II devices:	HER2 (IHC, FISH)
	MammaPrint
	ER, PR
IDE:	MammaPrint44K
	Her2 (RPMA, 44K-microarray)

New agents will be tested in both arms

An adaptive design will improve these assignments as the trial proceeds, benefiting patients.

Completed Projects (1)

The Utility of Adiponectin as a Biomarker for Predicting Glycemic Efficacy

Approved: October 2007 -- Status: Completed in January 2009

- Can the protein adiponectin serve as a *predictive biomarker* for glycemic control in Type II diabetes patients being treated with peroxisome proliferator-activated receptor agonists (PPARs)?

- Four pharmaceutical companies *(Merck, Eli Lilly, Roche, GlaxoSmithKline)* provided *pre-existing data from clinical trials* to third-party independent statisticians (Quintiles and NIDDK) who pooled, standardized, and analyzed blinded data to determine whether a relationship between adiponectin and glucose or HbA1C levels could be established.

- This data sharing project found that adiponectin was a robust predictor of glycemic response to PPAR agonists in Type II Diabetic Patients, but also in healthy individuals.*

*The results were presented at the American Society for Clinical Pharmacology and Therapeutics meeting in March 2009, at the American Diabetes Association meeting in June 2009, and are published in the July 2009 issue of Clinical Pharmacology and Therapeutics.

Adiponectin Results Highlights

- Project Goal: Determine whether adiponectin has utility as a predictive biomarker of glycemic control in normal non-diabetic subjects and patients with Type II diabetes
- Adiponectin is a robust predictor of glycemic response to PPAR agonists, but not non-PPAR drugs, in T2D patients
- Previous findings about the relationship between adiponectin levels and metabolic parameters (HbA1C, HDL, hematocrit) were confirmed by this analysis
- The potential utility of adiponectin across the spectrum of glucose tolerance was demonstrated
- This project established an approach to cross-company collaboration that embodies a robust, feasible approach to future biomarker qualification

Active Projects

FDG-PET Lung and Lymphoma Projects

FDG-PET Imaging in Non Hodgkin's Lymphoma to Predict Tumor Response to Treatment

Phase II Study of FDG-PET/CT as a Predictive Marker of Tumor Response and Patient Outcome: Prospective Validation in Non-Small Cell Lung Cancer

Project Goals:

- Determine the linkage of FDG-PET to the effect of therapy and drugs on clinical outcome and survival in lymphoma and lung cancer
- Develop standard protocols for acquiring and evaluating FDG-PET data
- Evaluate robustness and clinical feasibility of protocols

Value:

- More efficient drug development
- Inform the regulatory review process and approval path
- Better early response criteria
- Ability to cost-share the qualification of FDG-PET

Active Project

Carotid MRI Reproducibility Study via an NHLBI AIM-HIGH Ancillary Study

Project Participants: University of Washington, NHLBI, Abbott, Merck, Pfizer, FDA

Project Goals:

- Establish a standardized carotid MRI protocol at 15 centers with 3T whole body MRI scanners (using GE and Philips scanners)
- Provide training and standardized imaging sequences and carotid phased-array coils to all sites
- Add reproducibility scan at all sites (n=80)
- Determine the impact of site and platform on reproducibility

Project Duration and Budget:

- 18-month, $957K study from 3 private funders ($1.02M provided by NHLBI)

Dissemination of Results: Results to be submitted for publication first and then posted on The Biomarkers Consortium website

Active Project

Use of Targeted Multiplex Proteomic Strategies to Identify Plasma-Based Biomarkers in Alzheimer's Disease

Need:

- Simple biochemical tools to identify early AD and monitor treatment effects on disease progression

Opportunity:

- Utilize plasma biofluids from the Alzheimer's Disease Neuroimaging Initiative (ADNI) approved for use in assessing the utility of existing AD biomarker panels as tools for disease progression and identification of early AD

Objectives:

- Qualify known plasma-based biomarkers
  - Indicate change in disease progression
  - Serve as useful endpoints to be modified by drug treatment
  - Support disease modification drug trials

Strategies:

- Qualify plasma-based (151 analytes) multiplex panel composed of a subset of biomarkers identified in prior proteomic studies (next phase of project (CSF) to be pursued in 2009)
- Characterize the aβpeptide species present in plasma

Project Duration/Budget: 6 months / $0.4M

- Results available by April 2009 – funds available in-house at FNIH to conduct this project

Active Project

Comparison of Two PET Radioligands Labeled with ^{11}C or ^{18}F to Quantify the Peripheral Benzodazepine Receptor

Need: New radioligands with higher specific binding to PBR -- Limits to [^{11}C](*R*)-PK 11195 (prototypical tracer):

- low brain uptake, causing poor signal-to-noise
- amounts of specific binding too low for stable quantitative analysis
- study results difficult to interpret

Opportunity: Two new radioligands, [^{11}C]PBR28 and [^{18}F]FBR, have shown significantly higher specific binding to PBR than [^{11}C](*R*)-PK 11195 in preliminary studies

Objective: Develop improved, more sensitive and more quantifiable radioligands

Project Goals:

- Assess the utility of these two radioligands to image and quantify inflammation in the periphery and the brain in Alzheimer's Disease and Atherosclerosis
- Determine the time course/role of inflammation in different brain disorders/periphery and utility as biomarkers to assess the efficacy of agents designed to increase/decrease inflammatory markers

Project Duration and Budget:

- Two years, $1M (to be equally funded by NIMH/private sector – 6 companies) – launched in Q1 2009

Dissemination of Results: All results will be published via peer-reviewed journal and/or Consortium website